

175:., 1135-1138, 1992). Therefore,  $\alpha_v\beta_3$  antagonists can be useful therapeutic targets for treating such conditions associated with neovascularization (Brooks et al., *Science*, **264**: 569-571, 1994).

5       The  $\alpha_v\beta_3$  cell surface receptor is also the major integrin on osteoclasts responsible for the attachment to the matrix of bone. Osteoclasts cause bone resorption and when such bone resorbing activity exceeds bone forming activity, osteoporosis (a loss of bone)  
10 results, which leads to an increased number of bone fractures, incapacitation and increased mortality. Antagonists of  $\alpha_v\beta_3$  have been shown to be potent inhibitors of osteoclastic activity both *in vitro* (Sato et al., *J. Cell. Biol.*, **111**: 1713-1723, 1990) and *in*  
15 *vivo* (Fisher et al., *Endocrinology*, **132**: 1411-1413, 1993). Antagonism of  $\alpha_v\beta_3$  leads to decreased bone resorption and therefore assists in restoring a normal balance of bone forming and resorbing activity. Thus it would be beneficial to provide antagonists of osteoclast  
20  $\alpha_v\beta_3$ , which are effective inhibitors of bone resorption and therefore are useful in the treatment or prevention of osteoporosis.

PCT Int. Appl. WO 97/08145 by Sikorski et al., discloses meta-guanidine, urea, thiourea or azacyclic  
25 amino benzoic acid derivatives as highly specific  $\alpha_v\beta_3$  integrin antagonists.

PCT Int. Appl. WO 96/00574 A1 960111 by Cousins, R.D. et. al., describe preparation of 3-oxo-2,3,4,5-tetrahydro-1H-1,4-benzodiazepine and -2-benzazepine  
30 derivatives and analogs as vitronectin receptor antagonists.

PCT Int. Appl. WO 97/23480 A1 970703 by Jadhav,

P.K. et. al. describe annelated pyrazoles as novel integrin receptor antagonists. Novel heterocycles including 3-[1-[3-(imidazolin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2-(benzyl oxycarbonylamino)propionic  
5 acid, which are useful as antagonists of the avb3 integrin and related cell surface adhesive protein receptors.

PCT Int. Appl. WO 97/26250 A1 970724 by Hartman, G.D. et al., describe the preparation of arginine  
10 dipeptide mimics as integrin receptor antagonists. Selected compounds were shown to bind to human integrin  $\alpha_v\beta_3$  with EIB <1000 nM and claimed as compounds, useful for inhibiting the binding of fibrinogen to blood platelets and for inhibiting the aggregation of blood  
15 platelets.

PCT Int. Appl. WO 97/23451 by Diefenbach, B. et. al. describe a series of tyrosine-derivatives used as alpha v-integrin inhibitors for treating tumors, osteoporosis, osteolytic disorder and for suppressing  
20 angiogenesis.

PCT Int. Appl. WO 96/16983 A1 960606. by Vuori, K. and Ruoslahti, E. describe cooperative combinations of  $\alpha_v\beta_3$  integrin ligand and second ligand contained within a matrix, and use in wound healing and tissue  
25 regeneration. The compounds contain a ligand for the  $\alpha_v\beta_3$  integrin and a ligand for the insulin receptor, the PDGF receptor, the IL-4 receptor, or the IGF receptor, combined in a biodegradable polymeric (e.g. hyaluronic acid) matrix.

30 PCT Int. Appl. WO 97/10507 A1 970320 by Ruoslahti, E; and Pasqualini, R. describe peptides that home to a selected organ or tissue in vivo, and methods of

identifying them. A brain-homing peptide, nine amino acid residues long, for example, directs red blood cells to the brain. Also described is use of *in vivo* panning to identify peptides homing to a breast tumor or a  
5 melanoma.

PCT Int. Appl. WO 96/01653 A1 960125 by Thorpe, Philip E.; Edgington, Thomas S. describes bifunctional ligands for specific tumor inhibition by blood coagulation in tumor vasculature. The disclosed  
10 bispecific binding ligands bind through a first binding region to a disease-related target cell, e.g. a tumor

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